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## The Relevance of Patent Foramen Ovale to Type II DCS: An Overview of the Literature

**Joan Saary, MD, MSc**  
 Division of Occupational Medicine,  
 University of Toronto  
 61 Queen St. E., 8<sup>th</sup> Floor  
 Toronto, ON  
 Canada, M5B 1W8  
[joan.saary@utoronto.ca](mailto:joan.saary@utoronto.ca)

and

**Gary Gray, MD, PhD**  
 Defence and Civil Institute of Environmental Medicine  
 1133 Sheppard Ave W.  
 PO Box 2000  
 Toronto, ON  
 Canada M3M 3B9  
[gary.gray@dciem.dnd.ca](mailto:gary.gray@dciem.dnd.ca)

The significance of patent foramen ovale (PFO) in the pathophysiology of Type II decompression sickness (DCS) remains controversial. PFOs are common, occurring in approximately one quarter of the normal population, thus making right-to-left shunting of venous gas emboli (VGE) a theoretical concern in both hyper and hypobaric situations. Despite this high prevalence of PFO in the general population, and the relatively common occurrence of venous gas bubbles in diving and altitude exposures, the incidence of Type II DCS in diving or with altitude is remarkably low. Although the literature supports a relationship between the presence and size of PFO and cryptogenic stroke, and an increased relative risk of Type II DCS with a PFO in divers, the absolute increase in risk accrued is small. Hence, the value of screening is also controversial. This paper presents a brief summary of the literature on PFO's and DCS in altitude and diving, focussing on the latter; as well the analogous literature on cryptogenic stroke; and the results of an examination of the literature on detection of, screening for, and treatment of PFOs.

The foramen ovale develops as part of the process of atrial septation in which two apposed incomplete septa form with partially overlapping fossae. The foramen ovale represents the opening that remains patent between the septae. Post-natal increases in left atrial pressure usually force the interseptal valve against the septum secundum and within the first 2 years of life the septae permanently fuse due to the development of fibrous adhesions (1). However, autopsy studies have shown that in approximately 25% of cases in an adult population the foramen ovale fails to fuse (2).

This is generally of no significance since the higher left atrial pressure keeps the valve functionally closed. However, in situations where the right atrial pressure becomes significantly higher than the left, a gradient reversal can occur, causing right-to-left shunting through the foramen. Gradient reversal can occur when pulmonary vessels are obstructed (e.g. from overload of venous bubbles), when left atrial pressure is decreased (eg. after vasoconstriction causes increased pulmonary vascular resistance and subsequent decrease in cardiac output), on release of Valsalva or with strain, coughing, negative pressure breathing, cessation of positive pressure breathing, restricted breathing, or any other situations leading to substantial increase in venous return to the right heart. Such situations are common in both diving and air operations, including anti-G straining maneuvers, Valsalva for pressure equalization, and positive pressure breathing. Moon et al (3) speculate that immersion in water might increase a shunt as a result of increased right atrial pressure and cardiac dilation, and that the prevalence of shunting in divers may therefore be underestimated by assessments performed in the lab.

In some cases, right-to-left shunting has been shown to occur occasionally during quiet breathing without complication (4-6) and generally such intermittent shunting in a normal individual may cause transient decreased oxygen saturation, but little else. Of greater concern is when right-to-left shunting causes paradoxical embolization to occur. A patent PFO is a potential conduit for vessel-obstructing material such as blood clot in the case of stroke, or venous gas bubbles. However, there has been considerable controversy about the significance of a PFO as a possible mechanism for Type II decompression sickness.

Decompression sickness is a syndrome considered to be due to the presence of blood or gas in the tissues as a result of reduction in ambient pressure, resulting in a variety of symptoms depending on the location of the blood or gas. Gas entering the arterial system as a result of overpressurization of the lungs (pulmonary barotrauma) results in arterial gas embolism. Because overlapping pathologic mechanisms may result in confusion as to cause, the term decompression illness has come into favour as a descriptive term to cover all manifestations of decompression barotrauma and/or decompression sickness. In this paper, we use the term decompression sickness to refer to the syndrome due to

evolution tissue gas and venous gas emboli with right-to-left shunting as distinct from that caused by arterial gas embolism.

The phenomenon of paradoxical embolization has been well-studied among stroke patients, particularly among those who experience stroke despite having no risk factors. This situation is referred to as cryptogenic stroke. Although there are some studies which report that the prevalence of cerebral ischemia in PFO patients is not different from that in controls (7,8) in general, the prevalence of PFO has been shown to be higher among stroke patients than among controls (9,10). When classifying by the cause of stroke i.e. known cause, known risk factor, or no risks ie cryptogenic, the prevalence of PFO rises respectively (11-14).

Although PFOs are more common among both cause-known and cryptogenic stroke patients than in controls, the size of the PFO in cryptogenic stroke is generally larger than in cause-known cases (15,16) indicating an association between shunt size and risk of future embolic events, and suggesting that the clinical significance of individual foramina may be in part determined by echocardiographically identifiable characteristics.

It is clear that PFOs can lead to stroke if clot passes paradoxically through a functional right-to-left shunt, but the question remains whether one can now extrapolate what is known in the cryptogenic stroke situation to that of decompression. In fact, as early as 1969, reports existed suggesting that early neurological symptoms after diving could be caused by intracardiac shunts, and specifically by PFOs (17). Although gas emboli behave differently than clots in that they are not rigid and so can conform to vessel shape, their presence remains a key factor in the explanation of Type II decompression sickness.

In both diving and altitude, venous gas bubbles may develop when dissolved gas comes out of solution as the ambient pressure decreases during ascent, and the depressurized gas volume expands. The filtration of bubbles by the lung means they usually do not enter the arterial circulation. However, if the lungs are overwhelmed, or if there is a right to left shunt as would exist with PFO (or other atrial-septal defects) then venous bubbles could bypass the lung filter and directly enter the arterial circulation and thus travel to the brain.

Spencer (18) found that venous gas emboli were detectable in 4/11 divers (36%) after a no-decompression (USN tables) 18 m chamber dive for 60 min. He also noted that for the same profile, bubbles were more likely in open water rather than chamber dives. Later, Dunford et al (19) found venous bubbles in 17% of a sample of sport divers undertaking dives between 6 and 39 msw. Gas bubbles have been found in the venous circulation after ascents from as shallow as 3 m (20).

Eckenhoff et al (20) studied the dose-response relationship for decompression magnitude and endogenous venous gas bubble formation in humans. Subjects were exposed to pressure of 12, 16, and 20.5 fsw for 48 hrs then returned to surface in less than 5 minutes. There were no DCS cases but a large incidence of venous bubbling. Using the Hill equation to calculate the saturation depth pressure at which there is a 50% probability of detectable VGE, they found that with subclavian doppler 50% of humans would be predicted to generate endogenous bubbles after exposure to only 11 fsw.

Despite a clear relationship between decompression and development of venous bubbles, the relationship of VGE to DCS is less conclusive (21, 22). Recent and extensive work by Nishi at DCIEM (23) concludes that although large numbers of bubbles are not necessarily accompanied by DCS, the opposite is usually true i.e. DCS is usually accompanied by venous bubbles.

Pigs are increasingly being used in research because of their physiological similarity to humans particularly with respect to the cardiovascular system (24). In animal studies using pigs, Vik et al (25) investigated whether arterial gas was more likely when a PFO was present. The incidence of paradoxical air embolism tended to be higher in the PFO pigs compared to controls. In addition, less air needed to be infused (into the right heart) of the PFO pigs before arterial bubbles were seen. Finally, the size of the PFO was found to be unrelated to the occurrence of arterial gas.

They also tested the hypothesis that after rapid decompression pigs with a PFO would be more likely than those without one to have arterialized bubbles (26). Bubbles were found in all 6/6 of the PFO pigs, but only 2/8 in the non-PFO group ( $p < .009$ ). In addition, venous bubble counts in the PFO pigs were lower than in non-PFO pigs. Thus, arterial gas bubbles occurred at lower venous bubble loads in PFO pigs, and pigs with a PFO were more likely to have arterialized gas.

In a human population, Glen et al (27) used transcranial Doppler to determine the incidence of bubbles in the cerebral circulation of divers with and without PFO at various times during safe decompression from air dives. They found 4/17 divers with shunts identifiable by TCD, but none of the divers either with or without PFO had detectable bubbles in the cerebral circulation.

Considering that the prevalence of PFO in the population is about 25%, the incidence of Type II DCS is less than might be expected given the known prevalence of PFOs and the documented common occurrence of decompression-induced venous gas bubbles. Bove (28) calculated the frequency of military, sport, and commercial occurrences of Type II DCS to be 1.33, 2.52, and 2.09 per 10,000 dives respectively, with a combined frequency of 2.28 per 10,000 dives. Cross et al (29) note that of approximately 50,000 divers in Britain 15,000 (30%) might be expected to have a PFO, yet the number of neurological DCS cases per year is only about 100.

Much less research on the phenomenon of paradoxical gas embolism and the relationship between PFO and DCS has been reported in the altitude literature than in the diving literature so it will now be discussed first, the focus on the latter to follow. In fact, there has been some suspicion that DCS symptoms in altitude situations tend to be underreported to a greater extent than they do in diving due the perceived negative career-related consequences.

Because altitude DCS is related to decompression from saturation, it is thought that more venous bubbling occurs in altitude than with subsaturation decompression in diving, the result being a greater likelihood of paradoxical cross-over. Thus it is reasonable that one finds more cerebral symptoms among altitude than diving decompressions (30).

Clarke & Hayes (31) examined the prevalence of PFO among 24 cases of Type II altitude DCS in naval aviation personnel. They identified 4 cases (16%) of PFO by contrast TTE. They used Moon's (3) control data to conclude that there was no significant relationship between PFO and Type II altitude DCS.

Pilmanis et al (32) presented the first documented right-to-left shunting of venous bubbles after exposure to altitude. Retrospective examination of a 1500-subject database identified 6 subjects who demonstrated left ventricular gas emboli. Despite known embolization, PFOs were found in only 2 of the 3 cases investigated with TEE. In light of the fact that in all cases the venous gas score was high at the time of embolization, overload of pulmonary filtration was a second suspected mechanism for arterialized gas. The conclusion was that situations which expose subjects to altitudes known to produce high venous bubble loads should therefore be avoided.

Webb, Pilmanis, and O'Connor (33) went on to determine at what altitudes high bubble loads occur. They exposed 124 subjects to altitudes ranging from 11,500 to 25,000 feet for 4 to 8 hours, monitoring for DCS and venous bubbling. Venous bubbles were first seen at 15,000 ft and were present in 70% of cases above 22,500 ft. In terms of DCS symptoms, the 5% threshold for symptoms was 20,500 ft with an abrupt increase in symptoms beyond 21,200 ft. These results led the authors to recommend reconsideration of current US altitude exposure guidelines.

As previously mentioned, the suggestion that early neurological symptoms after diving could be caused by intracardiac shunts was made as early as 1969 (17). The majority of studies however were not undertaken to investigate this hypothesis until after 1986 when Wilmshurst et al (34) suggested that Type II DCS in a diver with an atrial septal defect (ASD) resulted from venous gas passing through the defect. If there was a right-to-left shunt as would exist with PFO then venous bubbles could directly enter the arterial circulation and migrate to the brain, particularly if the normal pressure gradient is reversed.

Unfortunately, there are several factors which limit the generalizability and hence the conclusions which can be drawn from studies that have attempted to determine the relationship between PFO and DCS in diving. These limitations include variation in study groups used (i.e. sport, commercial, or military divers), variation in control groups used (i.e. matched vs unmatched, diver vs non-diver), differing techniques for PFO detection (i.e. TTE vs TEE), and variability in definition of DCS or severity of cases selected to be members of the study group. Nonetheless, some trends occur in the examination of the findings of multiple studies although individually many studies have nonsignificant results.

First, the prevalence of PFO in non-DCS divers appears to be similar to that in the non-diving controls (35,36). Second, PFOs appear to be more common among DCS divers than non-diving controls (36,37). Third, PFOs seem to occur more commonly in divers experiencing Type II DCS than control divers (38,39). Finally, PFOs seem to be more frequent among divers with more serious DCS symptoms (3,38).

A meta-analysis of 3 previously published studies by Bove (28) mitigates some of the limitations of the individual studies by increasing the sample size. The results of this analysis show that the presence of PFO significantly increases the risk of all DCS in divers with PFO by 1.93 times compared to divers without PFO. For Type II DCS the risk was found to be 2.52 times higher in those with PFO.

Reconsidering Bove's calculation that PFO increases the risk for Type II DCS by 2.52 times; in a population of military divers in which the baseline incidence of Type II DCS is 1.33 per 10,000, an increase of 2.52 times 1.33 would lead to an absolute number of 3.4 per 10,000 cases of Type II DCS. With an absolute increase of 2 cases per 10,000, is screening for PFO warranted and if so what is the best screening method?

Although Bove (28) concludes that the absolute risk is small enough that screening is not warranted, and there is no basis for recommendations against diving in those with PFO, the decision to screen or not may vary based on the needs of a particular organization. In deciding whether or not to screen, one should also take into consideration the anticipated bubble load. With this in mind, screening of the shallow water sports diver is probably unnecessary, but in military or commercial divers, when high bubble loads are likely, screening might be useful. Any organization should consider following characteristics of a useful, albeit population-based screening measure prior to implementation (40).

- 1) Conditions for which screening is used should be important health problems i.e. The incidence should be sufficiently high that the cost of screening is not prohibitive.
- 2) Facilities for diagnosis and treatment should be available.
- 3) Effective, non-controversial treatment for patients with confirmed condition should be available.
- 4) Tests should have high sensitivity and specificity; screening must be safe, rapidly applied, and acceptable to the population being screened.
- 5) The natural history of the condition should be understood, such that if detection and treatment do not alter the natural history, screening should not be implemented.
- 6) Policy must stipulate what action will be taken in borderline cases to avoid overdiagnosis.
- 7) Maximum benefit for minimum cost must be achieved by comparing the costs and efficiency of various screening methods.
- 8) Control and screened groups should be compared at regular intervals to determine whether the screening procedure and subsequent investigations have an effect on the control group that is greater than just regular observation (placebo effect).
- 9) Compliance with screening recommendations should be ensured.
- 10) Screening programs should be a continuous process.

Should one then decide to go ahead with screening, transesophageal echocardiography (TEE), not transthoracic echocardiography (TTE) has been considered the gold standard for detection of PFO, although many other detection methods have been assessed. Generally any TEE modality is better than either contrast or colour flow TTE. Detection of PFOs with bubble contrast TEE is significantly better than with contrast TTE (12,41,42). With contrast TTE there tend to be more false negatives and undetermined cases than false positives, and most patients with a positive TTE study will also have a positive TEE. Thus an unequivocal contrast TTE study negates the need for further TEE imaging but a negative TTE does not. Among the different types of TEE examination, some studies suggest that bubble contrast detects more PFOs than does colour flow (8), whereas others suggest the opposite, that colour flow is better (42,43).

Although TEE provides better resolution than TTE, it is not without risks. These include esophageal injury, laryngospasm, aspiration, hypoxia, bronchospasm, dysrhythmias, and transient neurological side effects (44,45). Still, the morbidity rate of contrast TEE is only .07%, which is less than that of the exercise stress test, a well-accepted screening test, which has a complication rate of .09% (46). Nonetheless, TEE is generally considered an unpleasant procedure and IV sedation is often required. In addition, many find performing a Valsalva maneuver difficult with the probe in place.

Considering the low sensitivity of TTE and the relative complexity of TEE, a simpler, but acceptably sensitive method for PFO screening is transcranial Doppler (TCD). Studies comparing TCD of the middle cerebral artery to TEE demonstrate sensitivities ranging from 68 to 100%, with specificities repeatedly in the order of 100% (12,47-49). TCD is an ideal method for screening for PFO because the high sensitivity could spare patients a TEE exam. Furthermore, TCD costs less, and one can easily monitor effectiveness of the Valsalva by observing decreased cerebral blood flow (12). Other less well-studied methods of PFO detection which will not be discussed include carotid duplex monitoring (50), dye dilution and oximetry (51).

Studies evaluating PFO detection methods specifically among divers are few. Kerut et al (52) compared the ability of TTE, TEE and TCD to detect PFOs in both control subjects and divers referred for possible, probable, and definite neurological DCS. TEE was the most sensitive method for detecting PFOs in both controls and divers. However, only the TCD method of imaging differentiated between divers and controls. The authors suggest that the TCD method only detects clinically significant PFOs since only strongly positive TEE also had positive TCDs. They calculated the positive and negative predictive values for detection of shunts in DCS divers for all 3 imaging modalities. The positive and negative predictive value for each respectively was 52% & 59% (TEE), 62% & 58% (TTE), and 65% & 64% (TCD). Unfortunately the authors do not define "clinically significant" and in fact when "possible DCS cases" were removed from the sample, TCD no longer differentiated between DCS and control groups.

The implications of Bove's conclusions are that divers need not be screened prior to initiation of diving, and that those who already know that they have a PFO can still go ahead and dive. But what about the situation in which DCS has already occurred. Obviously, one must then consider evaluation for a shunt. If present, how does one reduce the risk of recurrent DCS in a diver with known PFO?

In Britain, professional divers with PFO are required to have transcatheter closure. Likewise the Allied Guide to Diving Medical Disorders published by NATO (53) states that "significant right-to-left shunts are incompatible with diving unless surgically corrected". Several risk reduction options to consider in PFO-positive divers include complete cessation of diving, reducing venous bubbling by either shallow diving only, altering the breathing gas used (eg choosing nitrox), or by using conservative decompression tables/methods, or finally closing the defect either by open surgery or by transvenous closure.

In the stroke literature, several methods of prevention of recurrent stroke have been used in patients with PFOs, which include no intervention, antiplatelet medications, anticoagulants, transcatheter closure, and surgery. Mas (54) argues that closure is the best option in cases of known paradoxical embolism.

Although surgical closure is easy to perform, it does not guarantee prevention of recurrence. Several studies have assessed open surgery as a method of closure. Giroud et al (55) studied 8 stroke patients and found no surgical complications, no recurrence of neurological events, and no residual shunting after PFO closure without post-op anticoagulation. Ruchat et al (56) also found no post-op complication among 32 patients, although residual shunts were present in 2/32 cases. Homma et al (57) followed 28 patients with a history of cryptogenic stroke and who underwent surgical PFO closure and found recurrence rate for neurological events of 19.5% overall. This rate was variable when age was considered and proportional hazards regression analysis revealed an increase in relative risk of recurrence of 2.76 per 10 years of age.

Nendaz et al (58) considered risk of stroke recurrence, complications, quality-adjusted life years, and death after 5 years in their decision analysis model assessing secondary stroke prevention options. They determined that if the risk of recurrence was .8 to 7% per year, defect closure was the best management strategy. At risk levels of .8% and 1.4% per year, anticoagulation and antithrombotic therapies were better than therapeutic abstention. If however, the risk of recurrence was low (i.e. less than .8% per year) then the best management option was no treatment.

Non-operative closure of atrial septal defects has been reported since 1976 (59,60). Transcatheter closure options are also possible for PFO and include button devices, clamshell umbrella devices and septal occluders (Amplatzer). Although the least expensive, the former method has been shown to have residual shunting (61), long recovery times, and higher numbers of complications compared to other methods (59). The double umbrella Clamshell had to be redesigned after device arm fracture in 71% of cases. Evaluation of the new version (Cardio SEAL) by Kaulitz et al (62) indicates improved device function, but in residual shunting in 57% of cases.

Formigari et al (59) report on the techniques and results of 28 ASD closures using three different percutaneous devices: the Sideris "Buttoned Device", the Das "Angel Wings", and the "Amplatzer". For all groups, fluoroscopy times were similar, but procedure time was shortest for the Amplatzer and longest for the buttoned device. Definitive closure occurred in all cases except 1 buttoned device. Followup times were longest for buttoned devices (at 40+- 2 months, compared with 27+- 2 mo for the Angel Wings, and 5+3 mo for the Amplatzer). In terms of complications, there were 2 cases of transient myocardial ischemia secondary to coronary air embolism in the buttoned devices, and 1 case of pericardial tamponade with the Angel Wings. Others have reported failures with this device also requiring emergency surgical intervention (63). There had been no complications with the Amplatzer device. Cost, was least expensive for the buttoned devices. Overall they concluded that the Amplatzer device is preferable.

Preliminary results of the World Study on closure with the Amplatzer from November 1998 (64) indicate that a total of 936 ASDs have been closed as well as 86 PFOs. Closure rates for PFOs are good, with 100% being closed at 24 hours, compared with 100% at 1 year for the ASD cases (98.9% at 1 month). There were 24 complications among these approximately 1000 patients, the majority of which included device embolization (9/24), TIA/embolization (4/24), and arrhythmia (3/24).

Wilmshurst et al (65) write about 2 cases of PFO in divers with neurological DCS who were successfully treated with an inverted adjustable button device, one with no residual and the other with a tiny residual shunt. Both divers returned to diving. There is no mention of whether either diver experienced repeated DCS post-procedure.

Closure by transcatheter methods remains impossible for some defects especially those greater than 25 mm in size. In addition there are relative contraindications for closure, particularly morphological constraints. Johnston et al (66) believe that wider application of invasive shunt closure methods should not occur before the relation between PFO and DCS is further delineated, noting that one must consider the shunt size and not just patency in DCS risk evaluation.

### Conclusions

In summary then, several conclusions can be tentatively drawn on the basis of available research:

- 1) Animal studies show increased arterial bubbles at lower venous bubble loads in pigs with PFO than in those without.
- 2) High bubble loads in either altitude or diving decompression increase the risk of pulmonary overload as a mechanism for arterial embolization.
- 3) There seems to be a relationship between cryogenic stroke and the presence of PFO, as well as the size of the PFO.
- 4) The weight of evidence favours an association between diving DCS and PFO. This association remains less clear in the case of altitude DCS, with less studies available on this topic.
- 5) The absolute increase in risk of DCS as a result of PFO seems small.
- 6) The issue of screening remains controversial and the decision to screen for a PFO should not be based on the absolute risk alone, but should also take into consideration decompression stress, professional status and employer responsibility, and the availability of adequate treatment.
- 7) For detection of PFO, contrast TEE is the gold standard, but as a screening tool, TCD in combination with contrast TTE is preferable to TEE.
- 8) Should closure be chosen for management, the transvenous Amplatzer appears to be the best available option, particularly for large PFOs.

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